Docket No.: CSIP-001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applic. No.	:	09/713,498 Confirmation No. 4672
Applicant	:	Zhao Chaoying et al.
Filed	:	November 15, 2000
Title	:	Novel Pharmaceutical Compositions for Treating and Saving and the Method for Preparation Thereof
Group Art Unit	:	1616
Examiner	:	John Pak
Docket No.	:	CSIP-001
Customer No.	:	24131

D E C L A R A T I O N under 37 C.F.R. § 1.132

In order to assist in the prosecution of this application and the traversal of the rejection of the claims by the Examiner, I, Zhao Chaoying, do hereby declare as follows:

I am a citizen of China.

I, Dr. Zhao Chao-Ying, am a Medical Doctor specializing in surgery. I received a degree in Medical Doctor from Second Military Medical University in 1994. Since that time, I have been employed as a doctor at Changhai Hospital in Shanghai

I have read the specification and claims of U.S. Patent Application No. 4,908,350 and the Office action dated June 25, 2004, in which claim 20 was rejected as anticipated by and being obvious over United States Patent No. 4,908,350 to Kramer et al. (hereinafter "Kramer").

I have personally conducted experiments to determine the effect of different concentrations of NaCl and Hydroxyethyl starch on hemorrhagic shocked dogs. My findings are attached hereto as Exhibit A in the form of six (6) tables of trial data and a brief discussion.

The trial data contained in the attached Tables 1 to 6, in combination with the results disclosed by Kramer, show that a higher concentration of NaCl, as suggested by Kramer, is not better. In fact, the opposite is true.

Table II of Kramer shows that different concentration of NaCl solution (from 300 to 3600mOsms) leads to different results. The figures therein for Cardiac Output (CO) is over the desired baseline only for groups having been administered at least 1800 mOsms when the hypertonic solution has been infused at 10 min, and for the group of 3600 mOsms when the hypertonic solution has been infused at 60 min. The values of CO in other groups are all below the desired baseline. This is especially true for Kramer's 300 and 1200 mOsms results.

Kramer explains that for the group administered with 3600 mOsms, convulsion occurred. Based upon the detrimental effects at 3600 mOsms, Kramer selects a preferred NaCl concentration of between 1800 to 2400 mOsms.

My experimental results, as shown in Table 3 of the Exhibit A, indicate that the affect of 7.5% NaCl (2400mOsms) is not as good as the affect of 5.3% NaCl (<1800mOsms) or that of 3% NaCl because the values of CO in the latter two groups are larger than the group of 7.5% NaCl. The document approving our medicine with a NaCl concentration under 1800 mOsms has been already issued by the concerned authorities in China.

I have undertaken a thorough review of the specification and amended claims of the instant application and conclude that the invention of the instant application is neither disclosed by nor suggested by Kramer.

Additionally, I have read the Office action dated June 25, 2004, in which claim 20 was rejected as obvious over International publication WO 98/08500 (hereinafter "WO'500").

WO'500 discloses a hypertonic composition containing L-arginine in addition to sodium chloride as low as 6% (w/v) [see page 5, lines 14 to 15, and claim 14], hetastarch (hydroxyl ethyl starch), and, of course, the injection liquid

[page 4, line 22].

In the compositions disclosed by WO'500, the L-arginine is present in the range of 0.3 to 7.5 g/100ml. The compositions of WO'500 are said to be superior to hypertonic saline solutions (7.2 to 7.5% NaCI w/v) and a 7.5% hypertonic saline 6% dextran solution [page 7, lines II-page 8, line 2] for the treatment of traumatic brain injury (TBI) and hypotension (shock) *because of* the presence of L-arginine. The L-arginine solutions of WO'500 are designed for the treatment of a patient having the combined injury of TBI and hemorrhage. TBI releases neuroexcitatory amines that increase the oxygen needs of the brain, while tissue swelling and intracranial hemorrhage increases the intracranial pressure (ICP) that reduces cerebral blood flow (CBF). WO'500 further notes that hypotension or reduced mean arterial pressure (MAP) further reduces brain CBF. See WO at 1/29 to 2/5. Accordingly, WO'500 sought a composition that, for a patient with combined TBI and hemorrhage, would, ideally, *lower* the ICP, selectively vasodilate the brain (but <u>not</u> other vessels of the body), and correct and prevent hypotension and hemorrhagic shock.

WO'500 achieved its invention by adding to a NaCI hypertonic solution (NaCI 6-8g/100ml) L-arginine in a range of 0.3-7.5g/100mo [See page 4, lines 9 to 11 and page 5, lines 12 to 15]. WO'500 did this to achieve reduction of ICP and

vasodilate the brain even though, L-arginine being a NO generation source, the addition of L-arginine would be expected to reduce to hypertonic saline solution's effectiveness for the correction and prevention of hypotension and hemorrhagic shock.

Hence, as can be seen from the description of WO'500, because L-arginine is converted by NO synthase, an enzyme in brain and blood vessels, into NO, which is a potent vasodilator (page 11, lines 21 to 24), L-arginine would be expected to lower the ability of a hypertonic saline solution to elevated the blood pressure in a patient experiencing hypotensive shock (page 3, line 30-page 4, line 2). Accordingly, this blood pressure lowering effect of L-arginine would seem to dictate a need to increase the NaCI content of the hypertonic saline solution to which it is added.

In any event, it is evident from WO'500 that L-arginine materially affects the basic characteristics of a hypertonic saline solution, *i.e.*, namely, the blood pressure elevating property of the hypertonic saline solution.

My invention is an improved hypertonic saline (NaCl) solution, with the improvement being a limiting of the maximum of free sodium ion in the solution to not greater than that of a 6.9% (w/v) NaCl solution. In my invention, the content of free

sodium ion in a hypertonic saline solution is reduced so as to lessen toxicity to the organism, and to reduce the rupture of blood cells and other side effects, while maintaining and/or enhancing its ability to increase the blood pressure of a person in shock by employing hydroxyethyl starch in conjunction with NaCl and generally in greater amounts than NaCl.

WO'500 is willing to suffer the negative effects of L-arginine upon the blood pressure elevating properties of a hypertonic saline-hydroxyethyl starch solution for the collection of hypotension and hemorrhagic shock to secure the beneficial effects that L-arginines exert upon the cerebral blood flow (CBE) and infracranial pressure (ICP) in the case of TBI. Nevertheless, it is axiomatic that inclusion of L-arginine materially affects the novel and basic characteristics of a hypertonic saline-hydroxyethyl starch composition of my invention.

The Examiner indicates a belief that L-arginine would not materially affect the novel and basic characteristics of my invention. Such a conclusion is unsupported and in error. In fact, inclusion of L-arginine the compositions of my invention materially affects their characteristics, *i.e.*, reduces their blood pressure restoring ability because L-arginine is a producer of the potent vasodilator NO.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: November 23, 2004

Signed: Zhao Chao-ying

Printed Name: Dr. Zhao Chao-Ying